Global Regulatory Policy

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Docket No. 2004N-0181 Critical Path Initiative; Establishment of Docket

Merck & Co., Inc. (Merck) is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's research and development pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

As a leading pharmaceutical company, Merck has extensive experience in thoroughly evaluating our products from discovery to approval and throughout their marketing life to ensure that they continue to provide health benefits with minimum risk. Therefore, we are well qualified to comment on the above referenced document (69 FR 21839). Please find below our comments regarding this important initiative.

Merck appreciates the opportunity to comment on this initiative and welcomes the chance to work with the Food and Drug Administration (FDA). We have detailed below ideas related to various aspects of the critical path, both in terms of the science and the regulatory structure needed to enhance the research and development of pharmaceuticals. We believe these ideas will improve our ability to work together to ensure that safe and effective products reach the market more efficiently.

Biomarkers – General

The use of exploratory biomarkers (those which have not yet been *validated* to serve as surrogate endpoints) in clinical development should be enhanced. We believe the Agency, through the Critical Path Initiative, can play an important role in encouraging the development of biomarkers. The Agency should foster an information exchange regarding what constitutes a valid biomarker, including information on the measurement of performance characteristics, which may include sensitivity, specificity, and reproducibility. Additionally, the FDA should make clear in what instances the sponsor can rely on valid biomarkers, for instance, to determine dose selection. For example, when developing a compound for atherosclerosis, would the use of hsCRP be appropriate during phase II to select a dose for proof-of-concept (POC) in an angiographic phase III study? We believe it is important for the FDA to clarify that the use of validated biomarkers is acceptable as an alternative to traditional approaches to dose selection and

determination of POC, as well as ensure that a consistent process is used to make these determinations.

The FDA should also issue *Points to Consider* regarding the clinical validation or *qualification* of biomarkers, that is, recommend how best to demonstrate the connection between a particular marker and a clinical endpoint. Especially important is the distinction of a biomarker versus a putative surrogate, and the utility of a particular biomarker. By providing this type of guidance, the FDA will enable industry to consistently determine which biomarkers it considers clinically validated. This will allow industry to determine acceptable development strategies earlier, which will decrease overall drug development times.

To complement the above efforts, the Agency, possibly in coordination with industry trade organizations, should establish a list of valid preclinical and clinical biomarkers. The list could be based on data available on a product's label or in published literature, posted on the FDA's website, and updated regularly. A transparent process for the communication of valid biomarkers will enhance drug development from preclinical testing through Phase IV.

Biomarkers – Toxicogenomics

The FDA should advance the use of toxicogenomics as an early indicator of development success. As noted above, we recommend that the Agency establish a list of validated preclinical and clinical biomarkers, which should include preclinical biomarkers from gene expression studies in animals. This would allow researchers to associate a safety outcome with an expression signature, enabling sponsors to identify adverse events earlier in the development process. This will ultimately result in a decrease in the amount of time necessary to develop pharmaceuticals. While this area remains scientifically complex, both the FDA and the NIH (through the NIH Roadmap) identified genomics as one area in which further research and study is necessary. To that end, the NIH is committed to providing resources and expertise to this area, which would complement the efforts of the FDA and industry. We recommend that the FDA use the Critical Path Initiative as the framework for collaboration in this important research area.

Biomarkers - Patient Reported Outcomes

While we have identified areas above where the development process can be made more efficient, we would also like to highlight an area that may cause delays in drug development. We recommend that the FDA's guidance document regarding Patient Reported Outcomes (PROs), which is currently under development, recognize a potential for delay in product development. For example, if the guidance requires the development and validation of new PRO measures during development, studies will become more time consuming and burdensome, and therefore delay the drug development process. We believe the validation of the PRO should be allowed to occur within the early clinical trials (Phase I/II) in order to provide efficiency to the development process.

Primary Prevention of Disease Task Force
The FDA and industry should create a joint task force to enhance the development of medicines for use in the primary prevention of disease. This effort may decrease the traditionally long review period for new drugs intended for prevention rather than treatment. The joint task force could consider such issues as regulatory barriers that impede the development of new medicines for the primary prevention of disease, policies that accelerate the development of new prevention-oriented drugs, or parameters that define an accelerated review process for disease prevention drug candidates based on biomarker data. This endeavor must include vaccines and encompass creative approaches to the developmental life-cycle of safe and effective vaccines that foster the use of validated surrogate immunogenicity endpoints for approval prior to the completion of long-term efficacy trials.

Trial Designs – Flexibility
The FDA should also advance the use and acceptance of flexible or adaptive trial designs prospectively, especially trials that occur in early development. Currently, clinical trials are planned well in advance of the trial completion dates. Prior to the completion of a trial, new data may be introduced or clinical practices may change, therefore prompting a reinterpretation of a study design by the Agency. This has made result-driven trials difficult and onerous to plan and implement. Clinical development would benefit if interim analyses were accepted throughout the trial. Following interim analyses, the trial design may be modified to include more (or less) patients. Of course, the analyses must be conducted in a manner that will not introduce bias nor put the overall study design at risk. Being more creative and allowing a flexible trial design based on the rollout of data will move Phase III trials forward more quickly.

Trial Designs – Multiple Endpoint Standards
The FDA should provide clarity and consistency with regard to setting multiple-endpoint requirements. For example, in studies for Alzheimer's and obesity, the FDA requires that several endpoints be met in a particular study. Thus, to achieve success, several primary endpoints must be positive. This increases the study size because companies must plan the study for the "weakest link," that is, since all of the primary endpoints need to demonstrate an effect, a study must be designed so that the endpoint that is the most difficult to show an effect is successful. While a smaller and simpler study would suffice for some of the targeted endpoints, a larger study must be designed per the Agency's requirements. Additionally, multiple endpoint requirements are not consistent among the review divisions, nor are they consistent between the various international review agencies. We believe that the Agency should collaborate with industry to streamline clinical trial requirements in order to provide consistency with respect to multiple endpoint requirements. Additionally, the Agency should collaborate with the various foreign review agencies through the ICH to ensure that multiple endpoint requirements are consistent internationally. By including stakeholders in these discussions, the setting of multiple-endpoint standards will become more consistent, which will make the drug development process more efficient.

Trial Designs – Non-inferiority Trials
We believe the FDA should provide guidelines regarding the process of setting margins for non-inferiority trials. Currently, we believe that setting non-inferiority trials is a practice of individual negotiation for a given therapeutic area. We understand that non-inferiority margin setting is assessed on a product-by-product basis. However, the industry would benefit from guidelines to follow while developing non-inferiority margins internally, prior to discussions with the Agency. Therefore, we request that the Agency provide *Points to Consider* to provide more clarity and consistency to the process of setting non-inferiority margins.

Combination Products
The industry commends the FDA's recent efforts regarding combination products and recommends that the Agency continue to promote this area. We believe the FDA should develop clear guidelines pertaining to the requirements for demonstrating the safety and efficacy of combination products. These guidelines should consider the following scenarios: 1) 2 or more marketed drugs are combined; 2) when a novel product is combined with a marketed product; and 3) when 2 novel products are combined.

Enhancing Review Practices
We recommend that the Agency finalize the guidance regarding good review management practices to set consistent guidelines for drug review. This is an essential area of interest to the pharmaceutical industry because changes in Agency personnel cause reinterpretations of regulations or guidance documents during drug review midstream. While good communication can overcome some of these issues, situations arise where regulatory interpretations change drastically when a reviewer leaves or is promoted. We believe a guidance document that sets a consistent voice across CDER's review divisions will resolve this issue and lead to more timely review decisions.

The Agency should also support efforts to increase collaboration between the FDA, academia, and industry to focus on new technologies or emerging areas of science that may make the drug development process more efficient. For instance, the FDA could support the development of academic curricula for training students at various educational levels (undergraduate to graduate) that will provide, upon graduation, a cadre of applicants for the Agency, academic institutions, and the industry to choose from for entry level positions up to senior science advisors. The Agency may also consider supporting a personnel exchange for agency staff to experience first hand what is involved in drug development from an industry perspective (from clinical decisions to analytical development) and for industry staff to experience the agency perspective. Allowing these personnel exchanges in a non-competitive, non-inspectional manner will foster a better understanding of the different perspectives, hopefully leading to a more streamlined drug development process.

ICH Harmonization
Lastly, the Agency should continue to collaborate with their colleagues in the EU and Japan to ensure that the harmonization of regulatory requirements continues. Through the ICH, the international regulatory community has demonstrated that a cooperative multi-lateral process for developing drug product review requirements and standards is a more economical use of resources for both the regulatory agencies and the industry.

Summary
Merck appreciates the opportunity to provide input to the Agency on this important initiative. We believe this is a significant opportunity for the FDA to work together with its stakeholders to identify valuable ideas that will enhance the drug development process. We have identified specific areas throughout the critical path which merit the attention of the FDA, the industry, and academia to improve drug development.

If we can provide further assistance, please do not hesitate to contact Brian Mayhew, Regulatory Policy Analyst, at 301-941-1402.

Respectfully submitted,

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